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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/446,628	09/19/2001	Mihael H. Polymeropoulous	31978-164334	2655

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EXAMINER
KAPUST, RACHEL B

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/446,628	POLYMEROPOULOUS ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- Th MAILING DATE of this communication appears on the cover sh t with th correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-73* is/are pending in the application.

4a) Of the above claim(s) *7-9,12-56 and 62-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10,11 and 57-59* is/are rejected.

7)☒ Claim(s) *5,6 and 60-61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☒ The proposed drawing correction filed on *15 August 2003* is: a)☐ approved b)☒ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (encompassing claims 1-6, 10-11, and 57-61) is acknowledged. The traversal is on the ground(s) there is not a substantial burden on the Examiner to examine Groups I and IV together.

Applicant's arguments have been fully considered but have not been found to be persuasive. As stated in the office action of paper no. 14, the different groups of nucleic acids and proteins represent different inventions and require different, non-contiguous searches, as evidenced by their different classification. They require separate searches of separate databases. A search for nucleotide sequences that encode a protein yields no comparison of that protein to other proteins; such comparison requires a separate search that yields no comparison of one polynucleotide sequence to another. Thus to consider both of these groups would constitute an undue burden because each requires considerations that are separate from each of the others.

The requirement is still deemed proper and is therefore made FINAL. Claims 7-9, 12-56, and 62-73 are withdrawn from consideration by the Examiner, 37 C.F.R. § 1.48(b).

Claims 1-6, 10-11, and 57-61 are under consideration.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined

claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Priority

It is noted that Applicants state that the current application is "based on provisional application number 60/505,684 filed June 25, 1997 which is relied upon and hereby expressly incorporated by reference herein" on p. 45 of the specification. However, the statement should be entered following the title of the invention or as the first sentence of the specification.

Information Disclosure Statement

The references cited in the Search Report received December 23, 1999 have been considered, but will not be listed on any patent resulting from this application because they were not provided on a separate list in compliance with 37 CFR 1.98(a)(1). In order to have the references printed on such resulting patent, a separate listing, preferably on a PTO-1449 form, must be filed within the set period for reply to this Office action.

Drawings

Substitute drawings were received on June 2, 2003 and August 15, 2003. The drawings were amended in order to comply with the sequence requirements. In order for the pre-grant publication to be as clear as possible, it is suggested that Applicants re-submit the as-filed drawings, and these will be the drawings that are published. In addition, it is suggested that Applicants amend the Brief Description of the Drawings for Figures 1 and 11 to incorporate the sequence identifiers within the specification as opposed to amending the drawings.

For instance, the sentence on p. 12 that reads "Amino acid translation of the exon is shown below the DNA sequence" could be amended to read "Amino acid translation of the exon is shown below the DNA sequence (SEQ ID NO: 25)." Similarly, on p. 15, in the description of Figure 11, the specification could be amended to add a sentence such as "Exons 1-2 are SEQ ID NO: 14, exon 3 is SEQ ID NO: 15, exon 4 is SEQ ID NO: 16, exon 5 is SEQ ID NO: 17, exon 6 is SEQ ID NO: 18, and exon 7 is SEQ ID NO: 19."

Specification

The disclosure is objected to because of the following informalities: on page 40, in the second paragraph, there are four primer sequences listed. However, none of the sequences are followed by their sequence identifier. Applicants are directed to 37 C.F.R. § 1.821(d)

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

In order to comply with 37 C.F.R. 1.821, appropriate correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see p. 33). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 10-11, and 57-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated human α-synuclein mutated to adenine at position 209, does not reasonably provide enablement for any mutated human α-synuclein or homolog thereof or any other mutation at position 209. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Applicants state that a homolog "is understood to mean any related gene or protein that is at least 25% homologous to the alpha synuclein gene or protein" (p. 16). Applicants further state that the term "mutation" is not limited to transition mutations, but can also mean a deletion, insertion or transversion (p. 18).

Applicants only list one mutation at base pair position 209 of the alpha synuclein gene which is a change from guanine to adenine (p. 6). Applicants have not provided any examples of other nucleotide substitutions or deletions that would lead to synuclein proteins that do not perform their usual or normal physiological roles. The nucleic acid sequence and correspondingly the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which nucleotides can be deleted or inserted or substituted is extremely complex and well outside the realm of routine experimentation, because

accurate predictions of a polypeptide's structure and function from mere sequence data are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, whereas other positions may be substituted or deleted without affecting the protein's structure/function relationship. Although Applicants state that a mutant alpha synuclein protein is meant to be only those proteins which do not perform their usual or normal physiological roles, and the term "mutant" is not meant to embrace sequence variants which encode proteins which are functionally equivalent to normal synuclein proteins (p. 19), a person of skill in the art would not know whether the protein performs its "usual or normal physiological roles" until the gene is cloned and expressed.

In addition, claims 4 and 59 are drawn to a nucleotide sequence that contains at least one mutation at base pair position 209. While Applicants teach that a change from guanine to adenine leads to a dysfunctional alpha synuclein protein, Applicants have not shown that other mutations at position 209 would also lead to a dysfunctional alpha synuclein protein. Changing the guanine to adenine at position 209 leads to a change in the amino acid sequence from an alanine to a threonine. If the guanine were changed to a cytosine or thymine, the alanine would be changed to a proline or a serine. Applicants have neither shown that a proline or serine at residue 53 would lead to a dysfunctional alpha synuclein, nor have they shown that the other mutations are linked to Parkinson's Disease. Again, one of skill in the art would not know whether the protein performs its usual or normal physiological roles until the gene is cloned and expressed.

Since detailed information regarding the structural requirements of the alpha-synuclein mutants and homologs is lacking, the state of the prior art, the unpredictability of the art, the lack of working examples, the breadth of the claims, and the lack of direction provided by the Applicants, it would require undue experimentation by one of skill in the art to practice the invention as claimed without further guidance from the instant specification.

Claims 1-4, 10-11, and 57-59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant disclosure of one mutant human α-synuclein does not adequately describe the scope of the claimed genus, which encompasses hundreds of thousands of different nucleotide sequences. As discussed above, the genus as disclosed by Applicants encompasses nucleotide sequences that are at least 25% homologous to SEQ ID NO: 1 and α-synuclein sequences wherein the mutation is a substitution, deletion, transversion, or transition. The specification defines the DNA sequences in terms of the function of the proteins that they encode. The specification at best enables and invites persons skilled in the art to identify those nucleotide sequences that encode proteins which function in the manner desired.

While Applicants teach the manner and means by which the nucleic acid molecules may be constructed (p. 26 and 30), one skilled in the art would not be able to visualize or recognize the identity of the full scope of nucleotide sequences claimed. Neither the functional characteristics of the proteins encoded by the claimed DNA nor prior art knowledge of the structure of the nucleotide sequences which encode the proteins allow persons of ordinary skill in the art to visualize or recognize the full scope of the biological materials claimed.

In order to visualize or recognize the full scope of the biological materials claimed, a person of ordinary skill in the art is required to perform one or more tasks, utilize one or more skills, to determine the complete identity of those biological materials reasonable expected to perform the functions the claims require, obtain those materials, and confirm their expectations for those materials. Only after persons skilled in the art prepare new DNA and test the encoded protein for functionality will they know whether Applicants would have the right to exclude them from making and using the new DNA constructs that they prepared. Therefore, the specification does not provide an adequate written description of the subject matter claimed.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3 and 57-58 are rejected under 35 U.S.C. 102(a) as being anticipated by Xia *et al.* (1996, *Ann. Neur.* 40(2): 207-215). Xia *et al.* teach an isolated α-synuclein nucleic acid comprising a polymorphism (see Fig. 1 and p. 212). Thus, claims 1-3 and 57-58 are anticipated by Xia *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Xia *et al.* as applied to claims 1-3 and 57-58 above. Xia *et al.* teach a mutant human alpha-synuclein nucleotide, but they do not teach a vector comprising said nucleotide. It is a common technique to take isolated nucleotide sequences and engineer them into recombinant vectors (see for example Bormann *et al.* (1996), *J. Bacteriology* 178(4): 1216-1218 and Kressig *et al.* (1996), *Nuc. Acids Res.* 24(21): 4358-4359). It would have been obvious to one of skill in the art to take the sequence taught by Xia *et al.* and use it to make a recombinant vector and transform cells with the vector for either replication purposes or protein expression purposes. Moreover, one of skill in the art would have expected to be successful at engineering the recombinant vectors and transforming cells with the vectors. Therefore, claims 10 and 11 are *prima facie* obvious over Xia *et al.*

Allowable Subject Matter

Claims 5, 6 and 60-61 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 1-4, 10-11, and 57-59 are rejected and claims 5, 6, and 60-61 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (703) 305-0634. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RBK